

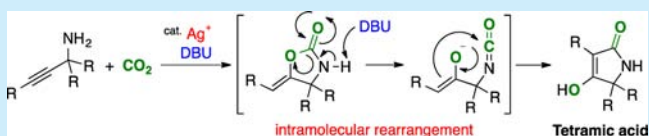
Novel Method of Tetramic Acid Synthesis: Silver-Catalyzed Carbon Dioxide Incorporation into Propargylic Amine and Intramolecular Rearrangement

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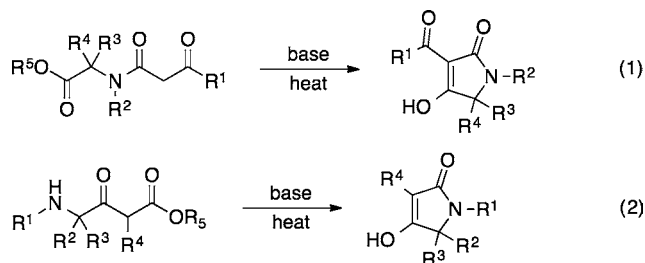
S Supporting Information

ABSTRACT: Tetramic acid derivatives have been studied as biologically active heterocycle structures for pharmaceutical or agricultural chemicals. Conventional preparative approaches often require highly functionalized starting materials and harsh heating conditions in basic media. The present report provides a conceptually new synthetic strategy for the synthesis of tetramic acid derivatives from easily available propargylic amines and carbon dioxide with a silver salt and DBU under mild reaction conditions.



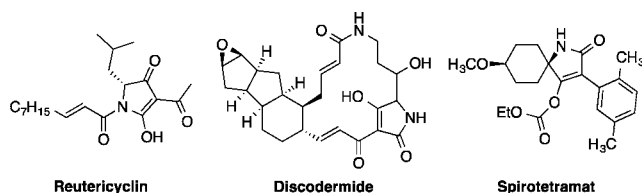
Tetramic acid structures are found in natural products known for their biological activity. For example, reutericyclin inhibits Gram-positive bacteria,¹ and discodermide inhibits the growth of *Candida* fungi.² In addition, spirotetramat has been used as an agricultural chemical.³ Therefore, much effort has been expended on the preparation of tetramic acid derivatives.⁴ Most have been synthesized through intramolecular cyclization via conventional Dieckmann condensation (Scheme 1, eq 1)⁵ or amidation (eq 2).⁶ These are

Scheme 1. Conventional Preparation of Tetramic Acid

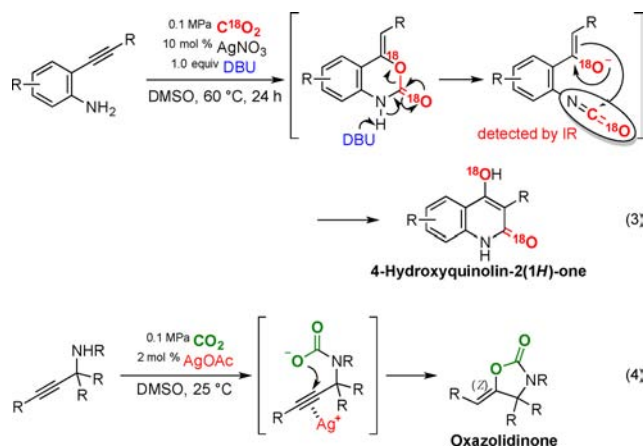


established strategies for preparing tetramic acids. However, highly derivatized starting materials are required and the reaction conditions involve high heat in basic media. Therefore, new synthetic alternatives are needed. Recent studies have investigated intramolecular aza-anti-Michael addition,⁷ enantioselective cyclization through samarium(II) iodide mediated coupling,⁸ reductive cyclization with samarium(II) iodide,⁹ and oxidative cyclization with hypervalent iodine compounds.¹⁰

Recently, we reported a transformation of *o*-alkynylaniline derivatives into 4-hydroxyquinolin-2(1*H*)-one derivatives via silver-catalyzed alkyne activation and a curious intramolecular rearrangement (Scheme 2, eq 3).¹¹ The proposed reaction mechanism involved generation of the corresponding benzoxazin-2-one through silver-catalyzed alkyne activation¹²



Scheme 2. Previous Works: Carbon Dioxide Incorporation into Alkynyl Amine Derivatives



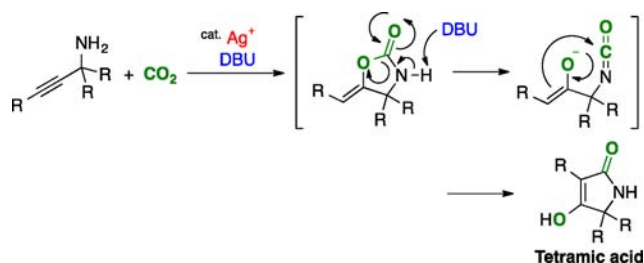
followed by intramolecular rearrangement with C–O bond cleavage triggered by deprotonation of the amide with DBU as a base. In mechanistic studies, isotopic labeling experiments with C¹⁸O₂ strongly suggested that the corresponding quinoline compound contained 1 equiv of carbon dioxide. In addition, a possible isocyanate intermediate was detected by *in situ* IR spectroscopy.

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This rearrangement was expected to be applicable to five-membered ring compounds to enable synthesis of tetramic acid derivatives from the corresponding primary propargylic amines. We have already reported a carbon dioxide fixation reaction involving propargylic amines which affords the corresponding oxazolidinone in the presence of a silver catalyst without any base (Scheme 2, eq 4).¹³ Conducting the reaction in the presence of an appropriate base and silver catalyst would be expected to generate an oxazolidinone that could undergo a similar rearrangement to produce the corresponding tetramic acid derivatives under mild reaction conditions from simple and common starting substrates (Scheme 3). The present report

Scheme 3. This Work: Silver-Catalyzed Carbon Dioxide Incorporation into Primary Propargylic Amines with Intramolecular Rearrangement



describes a novel method for the synthesis of tetramic acids, which relies on silver-catalyzed carbon dioxide incorporation, followed by an intramolecular rearrangement.

Previous reports^{11,12} have indicated that choosing the appropriate base is crucial for this reaction. Therefore, various bases were examined for suitability for the reaction (Table 1).

Table 1. Preliminary Experiment: Screening for Bases

entry	base	yield ^a (%)	
		2a	3a
1	K ₂ CO ₃	0	98
2	KOH	0	83
3	^t BuOK	0	97
4	Et ₃ N	0	89
5	DIPEA	0	91
6	DBU	94	trace
7 ^b	DBU	95	trace
8 ^{b,c}	DBU	95	trace

^aIsolated yield. ^bPressure of CO₂ is 0.1 MPa. ^cMeCN was used as a solvent instead of DMSO.

In the presence of inorganic bases such as K₂CO₃, KOH, and *t*-BuOK, the starting substrate was consumed completely, although the corresponding tetramic acid was not obtained; instead, the intermediate oxazolidinone was obtained in high yield (Table 1, entries 1–3). When triethylamine or DIPEA was used as a weak base, the corresponding product was not produced, but oxazolidinone was generated in 89% or 91% yield, respectively (Table 1, entries 4 and 5). When the sufficiently strong organic base DBU was used, the correspond-

ing oxazolidinone and propargylic amine were consumed and transformed into the desired tetramic acid in 94% yield (Table 1, entry 6). Moreover, carbon dioxide pressure could be reduced from 1.0 MPa to atmospheric pressure (0.1 MPa), and the reaction also proceeded in easily handled MeCN, instead of DMSO, without any loss of product yield (Table 1, entries 7 and 8). Single crystal X-ray analysis confirmed the structure of compound 2a as the targeted tetramic acid derivative after transformation of 2a into 2a' by methylation with diazomethane (Figure 1).¹⁴

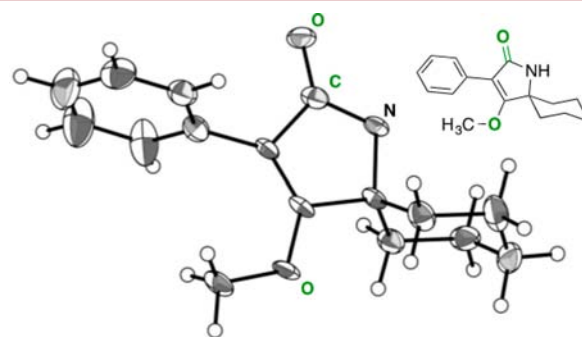


Figure 1. Single crystal X-ray analysis for 2a'. Thermal ellipsoids are shown at the 50% probability level. The compound 2a' was prepared by methylation of 2a with diazomethane.

Further optimization of the reaction conditions was performed (Table 2). When reaction temperatures were

Table 2. Conditions Optimization

entry	temp (°C)	base (equiv)	time (h)	yield ^a (%)	
				2a	3a
1 ^b	10	2.0	121	0	94
2 ^c	20	2.0	67	0	90
3	30	1.0	48	31	52
4	40	1.0	48	59	22
5	50	1.0	24	58	17
6	60	1.0	24	95	trace
7	60	2.0	4	92	0
8 ^d	60	2.0	24	96	0

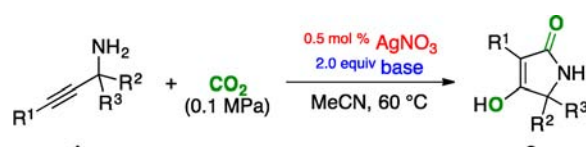
^aIsolated yield. ^b1.0 equiv of DBU was added after 84 h passed. ^c1.0 equiv of DBU was added after 31 h passed. ^dLoading of AgNO₃ was reduced to 0.5 mol %.

reduced from 60 °C to 10 or 20 °C, only the corresponding oxazolidinone was obtained in high yield without generation of tetramic acid, despite an excess amount of DBU and a longer reaction time (Table 2, entries 1 and 2). Reactions at 30, 40, and 50 °C afforded the corresponding tetramic acid; however, oxazolidinone also remained (Table 2, entries 3–5). Consequently, the reaction should be conducted at 60 °C to afford the desired product in high yield (Table 2, entry 6). These results suggest that the rate-determining step of the reaction is rearrangement of oxazolidinone triggered by deprotonation of the amide. Reaction in the presence of 2.0 equiv of DBU was

completed in just 4 h (Table 2, entry 7). Under the present reaction conditions, the catalyst loading could be reduced to 0.5 mol % (Table 2, entry 8) to produce the corresponding tetramic acid in excellent yield.

The optimized reaction conditions were applied to reactions involving various primary propargylic amine derivatives (Table 3). In the presence of 0.5 mol % of AgNO₃ and 2.0 equiv of

Table 3. Substrate Scope of Transformation of Various Propargylic Amines into Tetramic Acids with Carbon Dioxide Incorporation and Intramolecular Rearrangement



entry	time (h)	product	yield (%) ^a
1	24		96
2	24		49
3	1		90
4	48		85
5 ^b	24		58
6	4		87
7	2		96
8	8		98
9	6		93
10	2		90
11	48		92
12 ^{b,c}	7		91

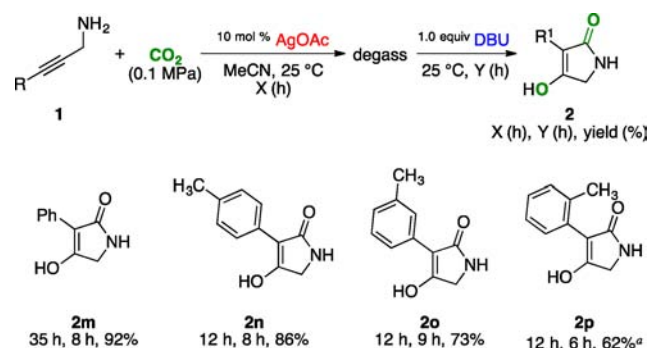
^aIsolated yield. ^bDMSO was used as a solvent instead of MeCN. 10 mol % of AgNO₃ and 2.0 equiv of DBU were used. ^cReaction mixture was exposed to 1.0 MPa of CO₂ without DBU for 1 h, then with added DBU and stirring for 6 h.

DBU under atmospheric pressure of carbon dioxide in MeCN, propargylic amine **1a** was converted into the corresponding tetramic acid **2a** in 96% yield (Table 3, entry 1). The propargylic amine with terminal alkyne **1b** also afforded the corresponding product **2b** in 49% yield (Table 3, entry 2). The effects of functional groups on the phenyl ring in substituent **R1** also have been examined.¹⁵ When a nitro group was placed

on phenyl group **1c** as an electron-withdrawing group at the *para*-position, the reaction proceeded quickly to produce the corresponding tetramic acid derivative **2c** in 90% yield (Table 3, entry 3). An electron-donating methyl group **1d** or methoxy group **1e** also was used as a substituent on the phenyl group at the *para*-position. Both reacted with carbon dioxide and were converted into the corresponding products **2d** and **2e**, respectively, in good yields (Table 3, entries 4 and 5). Heterocyclic groups also were investigated as substituents **R1**. Propargylic amines with a 2-pyridyl group **1f** or a 2-thienyl group **1g** on the alkyne underwent reaction to afford the corresponding heterocycle products **2f** and **2g**, respectively, in high-to-excellent yields (Table 3, entries 6 and 7). Alkynyl amines with a 1-naphthyl group **1h** or a 2-naphthyl group **1i** smoothly afforded the corresponding tetramic acid derivatives **2h** and **2i**, respectively, in high yields despite steric hindrance (Table 3, entries 8 and 9). Some substituents on the propargylic position **R2** and **R3** as well as on the alkynyl terminal were examined. Not only cyclohexyl amines like the model substrate but also the propargylic amine with a dimethyl group on the propargylic position **1j** could be transformed into the corresponding tetramic acid derivative **2j** in 90% yield (Table 3, entry 10). In addition, propargylic amines with a monosubstituent on the propargylic position underwent the reaction. Substituent **R2** was replaced with an ethyl group **1k** or phenyl group **1l**; both reacted with carbon dioxide to generate the corresponding products **2k** and **2l**, respectively, in 92% and 91% yield (Table 3, entries 11 and 12).

When propargylic amines with no substitution on the propargylic position were subjected to the reaction conditions, none afforded the corresponding tetramic acid derivative; instead the reactions resulted in complex mixtures. After optimization, a one-pot procedure was found suitable for these substrates. In the presence of silver acetate without DBU, the starting substrate was converted into the corresponding oxazolidinone by silver-catalyzed carbon dioxide incorporation, followed by degassing by freeze–deairation to remove dissolved carbon dioxide. To the reaction mixture at 25 °C, 1.0 equiv of DBU was added. Conducting this procedure using the starting substrate **1m** yielded the corresponding tetramic acid **2m** in 92% yield. Substrates with a methyl substituent in the *ortho*-, *meta*-, or *para*-position underwent reaction to produce the corresponding product **2n**, **2o**, or **2p**, respectively, in high yield (Scheme 4).

Scheme 4. One-Pot Carbon Dioxide Incorporation and Intramolecular Rearrangement of Propargylic Amines^a



^aThe oxazolidinone was isolated instead of the degassing process.

In conclusion, we have successfully developed a new strategy for the synthesis of tetramic acid derivatives. This reaction overcame previous obstacles encountered in synthesizing biologically or agriculturally significant heterocyclic compounds via alternative methods. A wide variety of substrates were applicable to the optimized reaction conditions to afford the corresponding tetramic acid derivatives in satisfactory yields. The results support a proposed reaction mechanism involving rearrangement ring opening with generation of an isocyanate and an enolate as intermediates triggered by deprotonation of the amide, followed by ring closure and formation of a new carbon–carbon bond. Further investigations and applications are currently being examined.

■ ASSOCIATED CONTENT

📄 Supporting Information

Experimental procedures and analytical data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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(14) Crystallographic data in this paper have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-962553. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

(15) When propargylic amines containing an alkyl group on the alkyne were subjected to the present reaction conditions, undesired side reactions occurred.